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High throughput formulation screening: Testing a novel two compartment microtiter plate approach

Ann-Christin Jacobsen[1], Martin Brandl[1], Annette Bauer-Brandl[1]

[1]Drug Transport & Delivery Group, Department of Physics, Chemistry & Pharmacy, University of Southern Denmark, Odense Denmark

CONTACT INFORMATION: annette.bauer@sdu.dk

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PURPOSE

A novel two compartment microtiter plate-based **high throughput formulation screening (HTFS)** approach was tested for its suitability for formulation performance ranking of enabling formulations.

Many new drug compounds have poor solubility and require complex formulation to enable oral administration. Identification of the optimum formulation design/composition can be a challenging and costly process, which may be bypassed by the present approach.

OBJECTIVES

The HTFS approach was tested using model formulations of **tadalafil (TDF)** with/without the amphiphilic polymer **Soluplus®** (crystalline and amorphous formulations). Formulations were evaluated with respect to both the amount of drug **dissolved** and the amount of drug **permeated**.

- Can the HTFS approach predict the formulation performance *in vivo*?
  → The *in vitro* HTFS results were compared to *in vivo* data from literature.
- How do screening parameters affect HTFS practicability and predictability?
  → The following test parameters were evaluated:
  1) Incubation time, 2) acceptor media and 3) dispersion (i.e. donor) media

CONCLUSIONS

The two compartment microtiter plate approach was generally able to predict the formulation performance *in vivo*.

Varying the screening parameters of the HTFS approach indicated that the protocol can be simplified to achieve high practicability and simultaneously high predictability.

FUTURE OUTLOOK

Testing the novel approach with other formulations of poorly soluble drug compounds will reveal it's usefulness in early drug development.

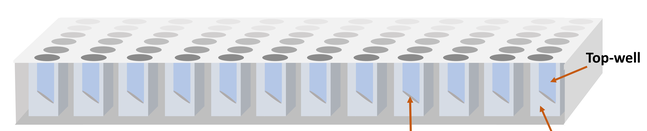

Figure 1 The two compartment 96-well microtiter plate.

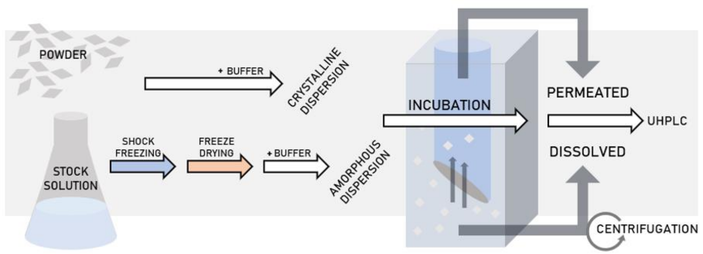

Figure 2 Flow diagram of the HTFS protocol.

METHODS

Figure 2 shows a flow diagram of the HTFS protocol used in all experiments.

- Four **TDF formulations** (i.e. suspensions) were prepared:

1) Crystalline TDF, 2) Crystalline TDF and Soluplus® (physical mixture), 3) freeze dried TDF and 4) 'co'-freeze dried TDF and Soluplus® (solid dispersion).

- Three **dispersion media** were used for the suspensions:

1) 50 mM phosphate buffer, 2) Simulated gastric fluid (SGF) and 3) Fasted state simulated intestinal fluid (FaSSIF).

- Five **acceptor media** containing surfactants were evaluated and compared to neat medium:

1) 1% Sodium dodecyl sulfate (SDS), 2) 0.2% d-α-Tocopheryl polyethylene glycol 1000 (VitE TPGS), 3) 1% VitE TPGS, 4) 0.2% Polysorbate 80 (PS 80) and 5) 1% PS 80.

300 µL suspension and 200 µL acceptor medium were transferred to the bottom-wells and top-wells, respectively, and incubated for 1, 3 or 6h. Figure 1 shows the assembled system. TDF concentration was determined via UHPLC.

RESULTS

In vitro in vivo correlation: Comparing the HTFS results to *in vivo* data from Krupa et al. 2016

Table 1 Coefficients of determination (R^2) when plotting the TDF concentration in either the donor compartment (dissolved TDF) or the acceptor compartment (permeated TDF) versus the *in vivo* AUC (Krupa et al. 2016). Incubation time: 6h, Acceptor medium: 1% VitE TPGS

Dispersion medium	R^2 (dissolved concentration vs AUC)	R^2 (permeated concentration vs AUC)
Phosphate buffer	0.8459	0.8499
SGF	0.826	0.8637
FaSSIF	0.8282	0.9391

A good *in vitro in vivo* correlation was achieved.

TDF concentration in the acceptor compartment (**permeated TDF**) generally yielded a **better prediction** at same time providing experimental ease (**no separation step**).

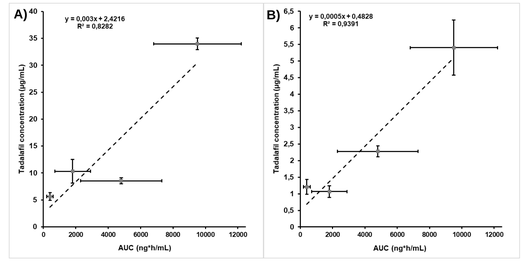

Figure 3 TDF concentration in A) the donor compartment (dissolved) or B) the acceptor compartment (permeated) vs *in vivo* AUC.

Influence of screening parameters

Acceptor media

Using surfactant solutions as acceptor medium increased TDF permeation as compared to neat buffer: *Sink conditions*

No difference between surfactants.

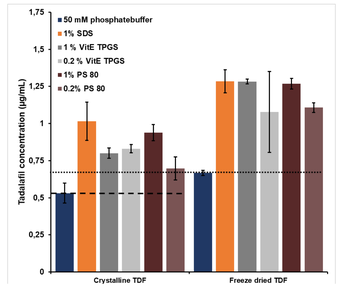

Figure 4 TDF concentration in the acceptor after 6h of incubation using different acceptor media. The dotted line indicates the TDF concentration when using neat buffer.

Incubation time

Steady TDF transport over the dialysis membrane for at least 6h. Longer incubation increased analytical ease.

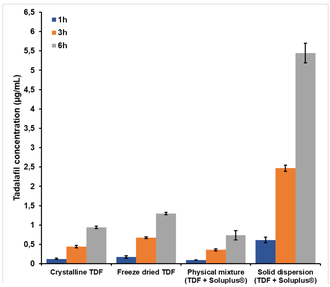

Figure 5 TDF concentration in the acceptor compartment after 1, 3 and 6h of incubation. Acceptor medium: 1% VitE TPGS.

Dispersion media

FaSSIF as dispersion medium yielded the highest TDF concentration in the donor compartment followed by SGF and phosphate buffer.

The same clear difference in TDF concentration could not be seen in the acceptor compartment.

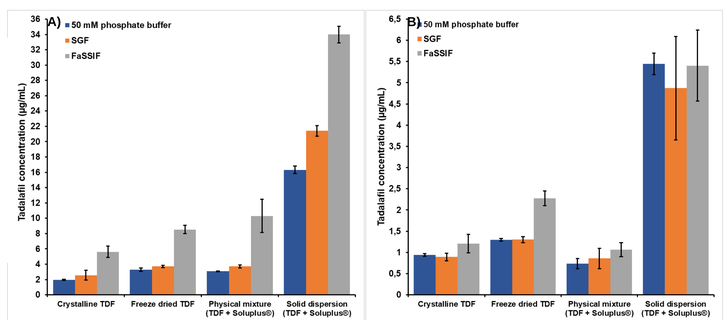

Figure 6 TDF concentration in A) the donor compartment or B) the acceptor compartment after 6 h of incubation using different media for dispersion of the formulations. Acceptor medium: 1% VitE TPGS

REFERENCES / ACKNOWLEDGEMENTS

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